

Lymphocytic Hypophysitis with Isolated Corticotropin Deficiency

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In a 32-year-old woman, acquired, isolated corticotropin deficiency resulted from postpartum lymphocytic hypophysitis. The literature suggests that lymphocytic hypophysitis may cause acquired deficiencies of anterior, and possibly posterior, pituitary hormones. Immunologic evaluation of our patient failed to uncover anticorticotroph antibodies. Prompt recognition of this potentially fatal condition is important because of the availability of effective treatment.

LYMPHOCYTIC HYPOPHYSITIS is considered to be an autoimmune endocrine disease (1) and often is associated with other autoimmune phenomena or with pregnancy. Acquired isolated deficiencies of pituitary hormones are not uncommon, and several authors have suggested that lymphocytic hypophysitis may cause them (1-11). In a few patients with suspected (7, 8) or proven (10) lymphocytic hypophysitis, antibodies to pituitary cells have been found. The findings that monoclonal antibodies may cross-react with the surfaces of several different endocrine cell types (12) and that corticotrophs may bind immunoglobulins via Fc receptors (13) make it more difficult to interpret the presence of these antibodies. When studied, most patients with isolated deficiencies of pituitary hormones have not had circulating immunoglobulins that react with human pituitary tissue. Thus, a link between lymphocytic hypophysitis and isolated deficiencies of pituitary hormones has not been firmly established.

In our patient, lymphocytic hypophysitis with isolated corticotropin deficiency and silent thyroiditis developed postpartum. No corticotrophs were found in biopsy tissue from the patient's pituitary gland; all other adenohypophyseal cell types were present.

Case Report

A 32-year-old woman had a 1-week episode of myalgias, anorexia, nausea, and vomiting during the eighth month of her first pregnancy. She recovered and 3 weeks later gave birth to a normal baby girl. The patient was able to breast-feed without difficulty, but 3 weeks after delivery she noted the gradual onset of anorexia, weakness, malaise, nausea, vomiting, and weight loss. At 3 months postpartum she was hospitalized by her family physician; at that time her serum calcium and total thyroxine concentrations were markedly increased. She was given saline intravenously and two intravenous doses of hydrocortisone and was transferred to a hospital in Rochester, Minnesota.

When seen here, the patient had normal physical findings,

aside from mild tachycardia and orthostatic hypotension; the thyroid gland was not tender. Laboratory evaluation confirmed significant hypercalcemia (14.8 mg/dL) and hyperthyroxinemia (Table 1). The hypercalcemia responded to intravenous administration of saline and did not recur when the infusion was stopped 4 days later. Endocrine evaluation confirmed thyrotoxicosis with decreased thyroid radioiodine uptake (Table 1), hyperprolactinemia, and hypocortisolemia with a low normal serum corticotropin concentration. The serum cortisol response to a single dose of corticotropin was subnormal (Table 1). A computed tomographic (CT) scan of the head showed a probable pituitary mass. The patient refused further tests and was dismissed with a prescription for prednisone, 5 mg/d orally, and the diagnoses of silent thyroiditis, probable pituitary mass, and probable corticotropin deficiency.

The patient did well at home but symptoms of hypothyroidism developed 1 month after her initial presentation. The hypothyroidism resolved without treatment (Table 1) 3 months later. Further testing 5 months after her initial evaluation confirmed the presence of secondary adrenal insufficiency (Table 1). Because amenorrhea and hyperprolactinemia continued and because another CT scan of the head showed a definite enhancing mass in the sella turcica, trans-sphenoidal pituitary exploration was done. Biopsy findings were consistent with lymphocytic hypophysitis (Figure 1A). Her postoperative course was uncomplicated, and she was dismissed with prednisone, 5 mg/d orally, prescribed. She became pregnant shortly after dismissal and was able to carry the pregnancy to term. No evidence of new pituitary or recurrent thyroid abnormalities was found during that pregnancy or after delivery.

Methods

PITUITARY BIOPSY EVALUATION

Pituitary tissue obtained at surgery was fixed in 10% neutral buffered formalin and processed for histologic and immunocytochemical study. The 5- μ m sections were stained by the hematoxylin and eosin, periodic acid-Schiff, and Gomori's reticulin methods. Serial sections were stained by the modified peroxidase-antiperoxidase method (14) for growth hormone (Dako Corporation, Santa Barbara, California), prolactin, corticotropin, follicle-stimulating hormone, luteinizing hormone, and thyrotropin. Normal adenohypophysis served as a positive control; substitution of normal rabbit serum for the specific primary antisera provided negative controls. Freshly obtained pituitary tissue was fixed in Trump's solution and routinely processed for electron microscopy.

Frozen sections prepared from a portion of the surgical specimen and from a normal pituitary gland (obtained at autopsy) that had been snap-frozen in liquid nitrogen were studied by direct cytochemical and immunocytochemical methods (15). Hybridoma antibodies were used to identify B cells (B1; Coulter Immunology, Hialeah, Florida), B cells and plasma cells (kappa and lambda immunoglobulin light chains; Becton Dickinson, Sunnyvale, California), and T cells (Leu-1 for pan-T cells, Leu-2a for suppressor and cytotoxic T cells, and Leu-3a for helper/inducer T cells; Becton Dickinson) (16). The presence of antipituitary antibodies was evaluated, as previously described (17), with an F(ab')₂ immunoglobulin fragment from

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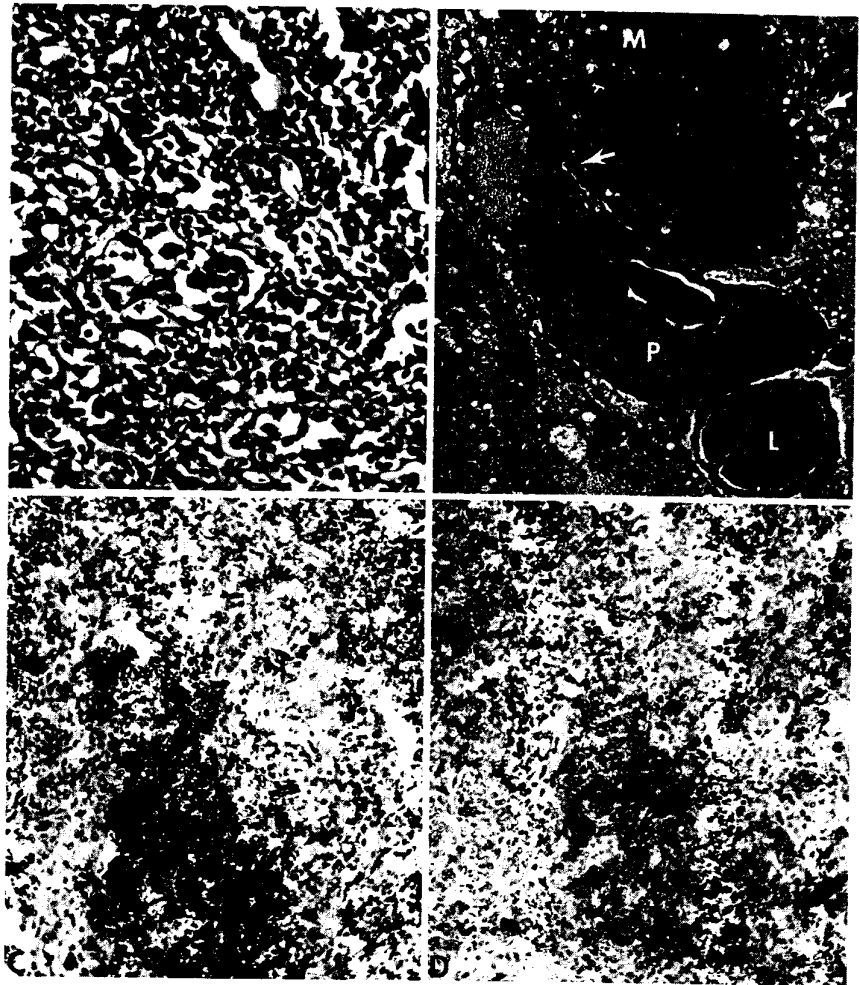
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Figure 1A. Anterior pituitary specimen showing lymphoplasmacytic infiltration, fibrosis, and resultant architectural disarray (hematoxylin and eosin; magnification, $\times 175$). Figure 1B. Electron micrograph showing infiltration of lymphocytes (L), plasma cells (P), and macrophages (M). Note degeneration of granulated adenohypophyseal cells, organelles of which are being phagocytosed (arrows) (magnification, $\times 5775$). Figure 1C. Immunoperoxidase preparation showing B cells (B1 monoclonal antibody) in a follicular compartment (bottom) (magnification, $\times 110$). Figure 1D. Immunoperoxidase preparation showing T cells (Leu-1 monoclonal antibody) in same field as panel C. Note that the follicular region (bottom) contains many T cells which, in separate preparations, were shown to be Leu-3a⁺.



the patient's serum.

Results

MORPHOLOGIC STUDIES

Sections of pituitary tissue stained with hematoxylin and eosin showed marked infiltration of the adenohypophysis by plasmacytoid lymphocytes, scattered histiocytes, and a few eosinophils (Figure 1A). Occasional germinal centers were seen. The architecture was intact, although fibrosis was noted. Immunocytochemical stains for somatotrophs, lactotrophs, gonadotrophs, and thyrotrophs revealed normal proportions of reactive cells. No corticotrophs were identified.

Ultrastructurally, no corticotrophs were noted, but other cell types were present. Inflammatory cells were intimately mixed with adenohypophyseal cells, some of which showed loss of continuity of cell membranes (Figure 1B). Phagocytosis of cellular debris was seen.

IMMUNOLOGIC AND CYTOCHEMICAL ANALYSES

A dense lymphoid infiltration of mixed B and T cells

was present in the anterior pituitary parenchyma. B cells were seen in well-defined follicles (Figure 1C). T cells were present in a Leu-3a/Leu-2a ratio of approximately 2:1; however, Leu-3a⁺ T cells were present exclusively within the follicular regions (Figure 1D). A modest number of scattered mast cells and small clusters of neutrophils were present in sinus regions apart from follicular areas. Monocytic/histiocytic cells were identified in sinusoidal regions, grouped in zones around degenerating parenchymal cells, and in close association with T lymphocytes of mixed subset. The normal pituitary control showed only scattered neutrophils within sinuses, rare mast cells, and rare plasma cells. With an F(ab')₂ fraction of the patient's serum immunoglobulin, we were unable to show antipituitary antibodies.

Discussion

Lymphocytic hypophysitis is now well recognized and considered likely to be a form of autoimmune endocrine disease (1). Our case shows that immune destruction of one pituitary cell line, with resultant failure of the target

Table 1. Clinical and Endocrinologic Findings over a 5-Month Period in a Patient with Lymphocytic Hypophysitis

	Normal Range	Initial Hospitalization					
		2/2	2/5	2/8*	2/10	2/11	2/14†
Thyroxine, $\mu\text{g/dL}$	5-12.5	14.0				11.8	
Thyrotropin, $\mu\text{U/mL}$	0.5-6.0			< 1.0			< 1/1/1.3
Thyroid radioiodine uptake, %							
6-hour	3-16			7			
24-hour	8-29			7			
Thyroid antibodies	< 1:100			0/0			
Plasma corticosteroids, $\mu\text{g/dL}$							
Morning	7-25		< 2.0	3.2			
Evening	2-14		< 2.9	3.4			
				3.1			
Corticotropin, pg/mL	< 120				24		
Urinary free cortisol, $\mu\text{g}/24\text{ h}$	24-108						
Prolactin, ng/mL	0-23		150				120/290/240
Estrogen, ng/mL	3-40		3.3				
Follicle-stimulating hormone, IU/mL	< 20		8.3				
Luteinizing hormone, IU/mL	< 30		5.4				

* Plasma corticosteroid levels measured before and 30 and 60 minutes after intramuscular injection of 250 μg of corticotropin.
 † Thyrotropin-releasing hormone stimulation test, 200 μg intravenously; serum thyrotropin and prolactin levels measured at baseline and 30 and 60 minutes after injection.
 ‡ Symptoms of hypothyroidism noted.
 § Corticotropin, 80 U intramuscularly every 8 hours.

organ, may occur while all other pituitary cell lines continue to function normally for extended periods of time. This patient's thyroid function returned to normal after she recovered from presumed transient lymphocytic thyroiditis. The ability to conceive and lactate after pituitary surgery adequately shows the integrity of the gonadotrophs and lactotrophs. Although several authors reporting on patients with acquired isolated deficiencies of anterior (2-7, 9, 11) or posterior (8) pituitary hormone have speculated on an autoimmune cause, our patient is the first in whom clinical endocrinologic evaluation and morphologic correlation of the pituitary lesion confirm this relationship. Among the 14 patients with morphologically confirmed lymphocytic hypophysitis whose cases are reported in the literature (1, 10, 11, 18-20), 2 patients had no corticotrophs (10, 11) and were clinically hypoadrenal. One of the patients was biochemically hypothyroid without increased serum thyrotropin concentrations (10), however; and the endocrinologic evaluation of the other patient consisted solely of thyroid function tests before death (11), although autopsy findings were consistent with isolated secondary adrenal insufficiency.

Isolated corticotropin deficiency has been reported in several patients with nonpituitary autoimmune endocrine diseases. Primary hypothyroidism appears to be the commonest associated endocrinopathy (4, 6, 21, 22), but transient lymphocytic thyroiditis (11, 23) and polyglandular failure (5, 24) have also been seen. Corticotropin deficiency has developed during or shortly after pregnancy (25-30), as has acquired isolated thyrotropin deficiency (31). Growth hormone deficiency (7), diabetes insipidus (8), and hypogonadotropic hypogonadism (9, 32) have been attributed to autoimmune phenomena on occasion. Portocarrero and colleagues (20) have suggested that the hyperprolactinemia associated with lymphocytic hypophysitis may be due to antilactotroph antibodies

(17), but a pressure phenomenon would best explain the hyperprolactinemia in our patient.

The inability to detect circulating antipituitary antibodies in our patient is not totally unexpected; antipituitary antibodies have been documented in only a few patients with suspected autoimmune hypophysitis (7, 10). Lymphocytic hypophysitis may be due primarily to a T-cell-mediated autoimmune attack on the pituitary gland. Enhanced T-cell reactivity to human pituitary extracts has been shown in a child with alopecia, candidiasis, primary immunodeficiency, and idiopathic hypopituitarism (33). The anterior pituitary infiltrate in our patient was composed of a well-organized chronic, but active, inflammatory process containing B cells (with follicle formation), Leu-3a+ and Leu-2a+ T cells, and monocyte/macrophages but only rare plasma cells. This immunologic picture is nonspecific with respect to which limb of the immune system (T cell or humoral) was primarily responsible for the destructive lesion.

In summary, lymphocytic hypophysitis may cause isolated corticotropin deficiency and may be responsible for acquired isolated deficiencies of other pituitary hormones. Whether the immune reaction related to this condition is primarily humoral or cell mediated is not yet clear. In persons at greater risk for lymphocytic hypophysitis (those with other autoimmune endocrine diseases or postpartum women) who develop a severe, unexplained illness, prompt administration of corticosteroids could be life-saving. The large proportion of autopsy reports emphasizes the need for diagnostic acuity.

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Table 1. (Continued)

	3/7†	6/2	Prolonged Corticotropin Stimulation Test‡			Pituitary Surgery	
			7/1	7/2	7/3	7/14	7/15
Thyroxine, µg/dL	3.8	6.3					6.5
Thyrotropin, µU/mL		<1.0					
Thyroid radioiodine uptake, %							
6-hour							
24-hour							
Thyroid antibodies		0/0					
Plasma corticosteroids, µg/dL							
Morning			3.8				
Evening							
Corticotropin, pg/mL							
Urinary free cortisol, µg/24 h				121	156		
Prolactin, ng/mL		31					4.4
Estrogen, ng/mL							
Follicle-stimulating hormone, IU/mL							
Luteinizing hormone, IU/mL							

national Institutes of Health for donating the corticotropin, follicle-stimulating hormone, and luteinizing hormone antisera; and Bio-Rad Laboratories, for donating the thyrotropin antisera.

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